UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/644,267	08/20/2003	Heather Lynn Davis	C1040.70012US00	6263

7590 01/22/2008

Helen C. Lockhart
Wolf, Greenfield & Sacks, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, MA 02210

EXAMINER
FALK, ANNE MARIE

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
01/22/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/644,267	DAVIS ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-53* is/are pending in the application.

4a) Of the above claim(s) *48-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/146,072.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/26/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed October 18, 2007 has been entered. Claims 32 and 38-53 have been amended.

The remarks filed July 5, 2007 (hereinafter referred to as "the response") are considered herein.

The elected invention is drawn to a method of inducing an antigen specific immune response in a subject by administration of an expression plasmid encoding a hepatitis B virus (HBV) antigen.

Claims 32-53 are pending in the instant application.

Claims 48-53 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention. Election was made **without** traverse in the reply filed on July 27, 2006.

Accordingly, Claims 32-47 are examined herein.

The objection to the oath/declaration is withdrawn in view of the newly filed declaration submitted February 26, 2007.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 32-47 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-14 of U.S. Patent No. 6,635,624. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the earlier-filed application are directed to a species that falls within the presently claimed genus. Thus, the claims of the patent anticipate the present claims (anticipation analysis).

At page 5 of the response, Applicants state that they may file a terminal disclaimer depending on the claims that are found to be allowable.

Accordingly, the rejection is maintained for reasons of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-47 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method as claimed, wherein the vector comprises a gene encoding the hepatitis B virus surface antigen protein, and further wherein the vector comprises a promoter operably linked to the gene, such that the antigen is expressed in the subject, does not reasonably provide enablement for the use of a vector encoding any HBV antigen. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a method of inducing an antigen specific immune response in a subject by administration of an expression plasmid encoding a hepatitis B virus (HBV) antigen.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, are set forth in *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988). These factors include: (1) the nature of the invention, (2) the state of the prior art, (3) the relative level of skill of those in the art, (4) the predictability of the art, (5) the breadth of the claims, (6) the amount of direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary.

Enablement has been evaluated giving due consideration to all the Wands factors, and the following factors are particularly noteworthy:

The state of the art of DNA vaccination is such that there are several significant limitations to the application of the same methodology in different species. Studies looking at the efficacy of DNA immunization using similar approaches in humans or large animals are "not encouraging" since DNA vaccines are "often less effective in large animals than in mice" (Babiuk et al., 2003).

In an article published well after the filing date of the instant application, Rubanyi (2001) teaches that the problems described above remain unsolved at the time the instant application was filed. Rubanyi states, "[a]lthough the theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far …" (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene expression control systems (see especially the section under "3. Technical hurdles to be overcome in the future", pages 116-125).

Beyond the technical barriers to all gene therapy approaches, each disease to be treated using gene therapy presents a unique set of challenges that must be addressed individually. The claimed methods encompass the use of a wide variety of genetic constructs to treat a wide variety of diseases. Rubanyi teaches, "each disease indication has its specific technical hurdles to overcome before gene therapy can become successful in the clinic (p. 131, paragraph 4). Rubanyi states, "the most promising areas for gene therapy today are hemophilias, for monogenic diseases, and cardiovascular disease (more specifically, therapeutic angiogenesis for myocardial ischemia and peripheral vascular disease…) among multigenic diseases" (p. 113, paragraph 4). As of the filing date of the instant application however, even the most promising areas presented barriers to successful gene therapy that could not be overcome by routine experimentation. Rather, the prior art shows that intensive investigation has met with limited success.

The court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970).

It is not to be left up to the skilled artisan to figure out how to make the necessary starting materials and then to figure out how to use them to produce the biological effects as recited in the claims. The courts held that the disclosure of an application shall inform those skilled in the art how to use applicant's claimed invention, not how to **find out** how to use it for themselves. *In re Gardner et al.* 166 USPQ 138 (CCPA 1970). This specification only teaches what is intended to be done and how it is intended to work, but does not actually teach how to do that which is intended.

Given the unpredictability in the DNA vaccination and gene therapy art, and further given that the specification fails to provide specific guidance on which antigens (and genes encoding them) can be used to produce a protective immune response treat, across the very broad scope, the skilled artisan would have

been required to engage in undue experimentation to develop a method within the scope of the claims for using any HBV antigen-encoding gene other than a gene encoding a surface antigen.

At page 6 of the response, Applicants assert that Babiuk demonstrates efficient expression of antigens from vectors expressing HBV and BHV in cattle and concludes that "various combinations of delivery systems can enhance immunity to DNA-based vaccines and make them practical for administration of these vaccines in large animals." Applicants conclude that Babiuk does not support the unpredictability of the invention. First, Applicants are reminded that a scope of enablement for the use HBV surface antigens has already been acknowledged. Babiuk et al. (2003) only teaches the use of gene gun delivery of hepatitis B surface antigen (HBsAg). The reference does not teach the use of any other HBV antigen and therefore does not demonstrate that the use of other HBV antigens was enabled at the time of the instant invention, which is October 1993, nor does the reference demonstrate predictability for the use of other HBV antigens. Contrary to Applicants contention, Babiuk et al. (2003) demonstrates that considerable experimentation was needed to develop vaccines suitable for use in large animals, given the problems acknowledged by those skilled in the art, and therefore amply demonstrates unpredictability in the art of DNA vaccination. In 2003, the studies reported by Babiuk et al. showed that gene gun delivery and the induction of mucosal immunity were superior to other modes of delivery of plasmid DNA for immunization of large animals and necessary for producing a protective effect. Absent the enhanced expression, protective effects were not seen. In contrast, in 1993, methods of DNA vaccination were in their infancy and little was known about the consequences of different routes of delivery and the biological effects of different DNA delivery techniques. Furthermore, for the reasons detailed below, the instant specification does not enable gene gun delivery of plasmids encoding antigens and the teachings of Babiuk et al. are specific to gene gun delivery. Babiuk et al. (2003) is post-filing art and therefore one of skill in the art would not have had the benefits of its teachings at the time of the invention. In 1993, there were no clear guidelines for improving the *in vivo* expression of an antigen from a plasmid vector to

achieve expression levels sufficient to produce a protective effect in large animals. Given the problems acknowledged by those skilled in the art, this is the epitome of unpredictability.

At pages 6-7 of the response, Applicants assert that the teachings of Rubanyi are not relevant to the claimed invention, that Rubanyi describes the unpredictability of gene therapy and is not applicable to the predictability of DNA vaccine technology. However, Rubanyi is cited for its teachings regarding technical hurdles hindering *in vivo* gene expression. Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene expression control systems (see especially the section under "3. Technical hurdles to be overcome in the future", pages 116-125). The field of gene therapy broadly includes any method that involves *in vivo* expression of an exogenously administered nucleic acid vector for production of a therapeutic effect, and is not limited to gene replacement techniques. Accordingly, the field of gene therapy is the appropriate field of inquiry concerning *in vivo* expression of exogenous DNA constructs.

At page 7 of the response, Applicants cite Kuhober et al. (1996) for describing the use of DNA immunization to induce antibody and cytotoxic T cell responses to hepatitis B core antigen in mice. While class I-restricted CTL responses to HBcAg were elicited, there is no evidence that the immune response would be protective. Mice are not susceptible to HBV infection and therefore challenge experiments are not possible in this system. Thus, the results do not demonstrate a protective immune response. In direct rebuttal to Applicants' arguments pertaining to the Kuhober reference, it is noted that immune responses in mice are not generally predictive of immune responses in other species. McCluskie et al. (1999, Molecular Medicine 5:287-300) teach that the strength and nature of the immune responses to administration of DNA vaccines varies between species and that it is not clear that results from one species are predictive in another (page 287 and Abstract). Given that immune responses in mice are not generally predictive of immune responses in other animal species, the results of the experiments described

in the reference of Kuhober et al. (1996) do not demonstrate that immunization with a vector encoding the HBV core antigen would be protective in any animal species, including humans.

At page 7 of the response, Applicants cite Haynes et al. (1996) for describing the use of DNA immunization to elicit antibody and cytotoxic T cell responses to hepatitis B in pigs, mice, and rhesus monkeys. Contrary to Applicants' contention, the reference does **not** describe the use of DNA immunization to elicit cytotoxic T cell responses to hepatitis B. With regard to hepatitis B, the reference teaches only the induction of antibody responses in DNA vaccination experiments. The results presented therein are specific to particle-mediated genetic immunization. In fact, the authors explicitly state that "[t]he observation that immunological results similar to those seen in rodents can also be achieved in larger animals is likely due to the physical nature of this delivery process" (page 41, column 1, paragraph 2). The instant specification does not describe or discuss particle-mediated methods of DNA vaccination at all. There is no mention or contemplation of the use of particle-mediated methods of DNA vaccination in the instant specification. The instant specification is directed exclusively to intramuscular administration of a plasmid vector encoding an HBV antigen. With regard to the genetic immunization of rhesus monkeys using a vector encoding the hepatitis B core antigen (HBcAg) driven by the CMV promoter, the results reported are specific to particle-mediated (gene gun) delivery of DNA to the skin. Furthermore, although HBcAg-specific antibody titers are reported, there is no evidence that the antibody response provided a protective effect. Given that the reference of Haynes et al. (1996) is post-filing art, the skilled artisan would not have had the benefits of its teachings of with regard to gene gun-mediated immunization of the skin at the time of the instant invention. Thus, it cannot be said that Haynes et al. (1996) provide evidence that the instant invention was enabled as of the effective filing date which is 10/22/93, for the foregoing reasons.

Haynes et al. (1996) further confirms the unpredictability for DNA vaccination in large mammals. The authors note the studies of Wolff and coworkers which demonstrated that direct muscle

inoculation of plasmid DNA resulted in low level, sustained gene expression in rodent muscle. However, gene expression following muscle inoculation in nonhuman primate muscle was demonstrated at a significantly reduced efficiency (page 38, column 2, paragraph 2). The authors further refer to the advantage of gene gun-based DNA vaccine technology as being particularly useful in "larger animals where the potential for muscle injection is less clear" (page 38, column 2, paragraph 3). The unpredictability in the art of DNA vaccination also extends to the particular route of administration used. In describing the use of particle-mediated DNA immunization to produce protective immune responses in mice, the authors note that "[p]arallel immunizations via the intramuscular, intravenous, intraperitoneal, and intradermal routes, using considerably greater amounts of DNA, did not achieve comparable levels of vaccine protection." Thus, results obtained in mice by gene gun methods are not predictive of results obtained using other routes of administration. The authors go on to report that "[a]dditional data comparing the relative efficacy of muscle injection and particle-mediated DNA immunization of the epidermis ... demonstrated that considerably stronger immune responses could be elicited against several antigens using as little as 16 ng of DNA per immunization. Intramuscular injection of as much as 6000-fold more DNA did not achieve comparable immune responses" (page 39, paragraph bridging columns 1-2). Thus, the results obtained by gene gun methods are not predictive of results obtained by intramuscular administration.

While the present claims cover the induction of both protective and non-protective immune responses, absent a protective immune response, the claimed method lacks an asserted utility. The instant specification provides an enabling disclosure only for a method as claimed, wherein the vector comprises a gene encoding the hepatitis B virus surface antigen protein, and further wherein the vector comprises a promoter operably linked to the gene, such that the antigen is expressed in the subject. The specification does not reasonably provide enablement for the use of a vector encoding any other HBV antigen.

At page 8, paragraph 2 of the response, Applicants allege that the discovery according to the invention that DNA vaccines are effective at inducing local expression of a sufficient amount of hepatitis B viral antigens to produce an immunoprotective response, applies generally to hepatitis B antigens. In direct rebuttal to Applicants' argument, it is noted that the prior art generally acknowledges the critical role of the particular antigen used in DNA vaccination protocols. In a review of genetic immunization, Ertl et al. (1996, Viral Immunology, 9(1):1-9) emphasize the critical role of the antigen, stating that, "although any antigens can be delivered by genetic immunization, some proteins upon expression by plasmid vectors remain immunologically silent. The principles that govern success versus failure of genetic immunization with regard to each individual protein remain to be elucidated" (page 2, paragraph 3).

At page 8, paragraph 3 of the response, Applicants assert that, prior to the instant invention, hepatitis B protein antigens derived from the core were well known and that the gene sequences for these antigens were also known. It is acknowledged that the core protein was described in the prior art. However, a written description of an antigen is not sufficient to provide an enabling disclosure for its use in producing a protective immune response by DNA vaccination methods.

Conclusion

No claims are allowable.

This application contains claims 48-53 drawn to an invention nonelected without traverse in the reply filed on July 27, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

/Anne-Marie Falk/
Primary Examiner, Art Unit 1632